

# Microwave-assisted synthesis of cycloalkanespirohydantoins and piperidinespirohydantoins as precursors of restricted $\alpha$ -amino acids

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DOI: <http://dx.doi.org/10.3998/ark.5550190.0012.221>

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## Abstract

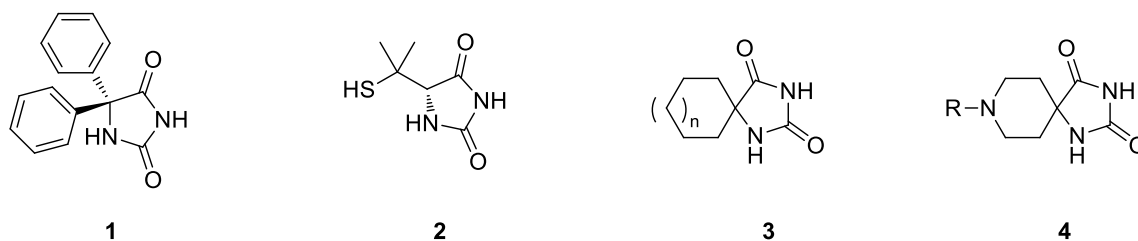
Cycloalkanespirohydantoins **3** and piperidinespirohydantoins **4** were synthesized from cycloalkanones **9** and piperidones **10** under microwave-assisted conditions. Results are compared with those obtained under thermal conditions. Cycloalkanespirohydantoins **3** were N-protected with Boc group and hydrolyzed under basic conditions to obtain five, six and seven-membered ring restricted  $\alpha$ -amino acids **12** in very good overall yields (76–94%).

**Keywords:** Microwave irradiation, cycloalkanespirohydantoins, restricted  $\alpha$ -amino acids

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## Introduction

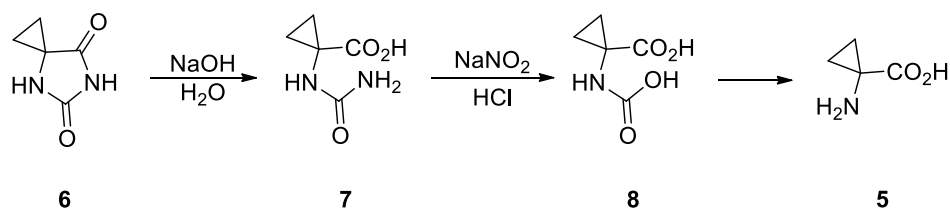
The imidazolidine-2,4-dione ring or hydantoin has been extensively studied. This five-membered heterocyclic ring containing a reactive cyclic urea core is present in a wide range of biologically active compounds.<sup>1</sup> For example, Phenetoin **1** (5,5-diphenylhydantoin)<sup>2</sup> was synthesized in 1908 and is the drug of choice for the treatment of certain types of epileptic seizures.<sup>3</sup> The biological activities that have shown some of their derivatives are mainly as anticonvulsant and antimuscarinic, antiviral, antiulcer and antiarrhythmic agents. Also, penicillamine hydantoin **2**, a pro-drug form of D-penicillamine, and its thiazolidine-2,4-dione derivatives have shown insulinotropic effects in INS-1 cells.<sup>4</sup> Some hydantoin compounds are potent inhibitors of muscle and liver glycogen phosphorylase, metalloproteinase and HIV protease enzymes. Hydantoins are also used as herbicides, antibiotics and as DNA binding compounds.<sup>5</sup> The observed activities arise from the hydantoin heterocycle, but the different ligands attached to it are determinant in these properties.<sup>6</sup>



The first synthesis of cycloalkanespirohydantoin was developed by Bucherer and Lieb in 1934 by the reaction of a cycloalkanone with sodium cyanide and ammonium carbonate refluxed in a mixture of ethanol/water.<sup>7</sup> Recently, Naydoneva and coworkers reported the synthesis of a series of cycloalkanespirohydantoin **3** with  $n = 0, 1, 2, 3,$  and  $7$  and yields of 89–95% using the Bucherer-Lieb conditions.<sup>8</sup> However, there is an inconvenience for this synthetic method from an experimental point of view. The use of cyanide ion and the high temperature required to obtain higher yields in the cyclization process can promote hydrogen cyanide and must be controlled to prevent the risk of intoxication or contamination.

In this sense, microwave irradiation in chemical reactions has been recognized for increased reaction rates, better yields and cleaner products.<sup>9,10</sup> Additionally, working with sealed vessels for shorter times reduces the exposure to toxic substances. Several methods for the preparation of diverse hydantoin have been reported using microwave-assisted conditions,<sup>11</sup> but to the best of our knowledge, the synthesis of cycloalkanespirohydantoin **3** and piperidinespirohydantoin **4** has not been reported under microwave-assisted conditions.

Restricted  $\alpha$ -amino acids, i.e. 1-aminocycloalkane-1-carboxylic acids with three, five, or six-membered rings have attracted considerable attention due to the variety of synthetic applications<sup>12</sup> and the conformational restriction induced for these molecules when they are incorporated into peptides reducing the flexibility of peptide chains.<sup>13</sup> In this sense, spirohydantoin are important intermediates in the synthesis of restricted  $\alpha$ -amino acids as well as in the evaluation of conformational properties of rigid cyclic glutamic acid analogues.<sup>14</sup> For example, the first synthesis of 1-aminocyclopropanecarboxylic acid **5** reported in 1922,<sup>15</sup> was accomplished by alkaline hydrolysis of cyclopropanespirohydantoin **6**, which was obtained by Hofmann degradation of the amide functionality in cyclopropane-1,1-dicarboxamide. Treatment of the resulting hydantoinic acid **7** with nitrous acid furnished carbamic acid **8**, which upon spontaneous loss of carbon dioxide formed aminocyclopropanecarboxylic acid **5** in 60% yield (Scheme 1).



**Scheme 1.** First synthesis of 1-aminocyclopropanecarboxylic acid **5**.

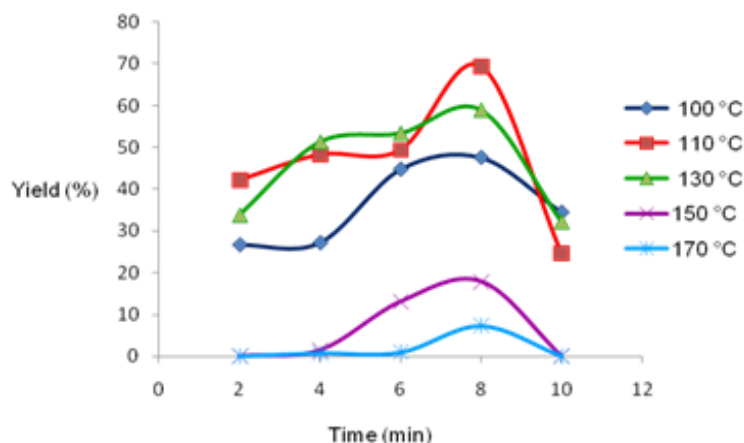
The traditional synthetic method for almost all restricted amino acids includes the conversion of a ketone into spirohydantoin via the classical Bucherer-Bergs reaction. Hydrolysis of

spirohydantoin leads to crude amino carboxylic acids.<sup>16</sup> The same methodology is used for the synthesis of 1-aminocyclobutane carboxylic acid. The most common approaches include the Strecker synthesis starting from cyclobutanone.<sup>17</sup>

In recent years, the cycloalkanespirohydantoin **3** were used as synthetic intermediates to generate restricted  $\alpha$ -amino acids in mild conditions.<sup>18</sup> The Bucherer-Berg approach is still the most convenient method to prepare simple restricted  $\alpha$ -amino acids in good yields.<sup>19</sup>

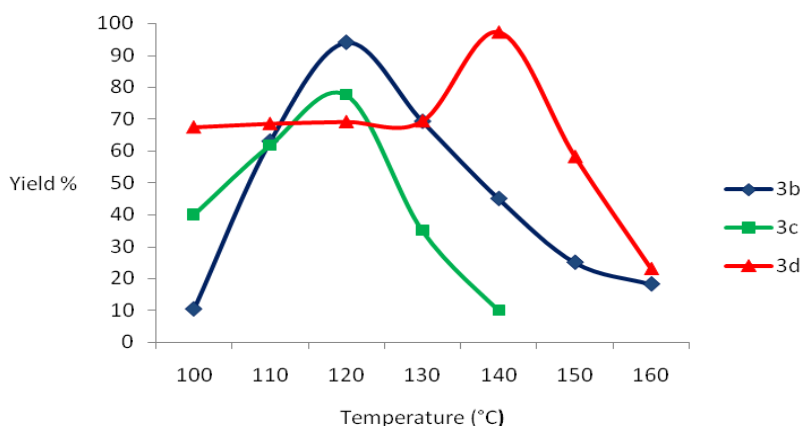
## Results and Discussion

We report the synthesis of cycloalkanespirohydantoin **3** and piperidinespirohydantoin **4** under microwave irradiation. Figure 1 depicts the study of yields for spirohydantoin **3b** depending on time and temperature. The best yields were obtained at 8 minutes for all temperatures; longer irradiation lowers the yields. The higher yields were obtained between 110 and 130 °C; yields were moderate at lower temperatures and poor at higher temperatures. Similar results were observed for the other spirohydantoin.



**Figure 1.** Study of the time dependence of yields for spirohydantoin **3**.

At the reaction time of 8 min, the maximum yield for spirohydantoin **3b,c** was found at 120 °C (Figure 2); for spirohydantoin **3d** the yield was 68% between 100–130 °C, but increased to 97% at 140 °C (Figure 2). At lower temperatures yields were low; higher temperatures caused decomposition.

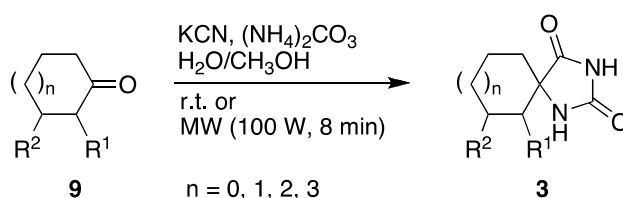


**Figure 2.** Study of temperature dependence of yields for spirohydantoin **3**.

For the synthesis of cycloalkanespirohydantoin **3**, the cycloalkanones **9a–f** were treated with potassium cyanide and ammonium carbonate under thermal and microwave irradiation conditions (Table 1). Under thermal conditions, low yields (16–59%) were obtained with five- and six-membered cycloalkanones (entries 1–4), while with seven- and eight-membered cycloalkanones, the yields increased to 87 and 100%, respectively (entries 5, 6).

The same reactions under microwave irradiation gave the opposite result: higher yields were obtained with five- and six-membered cycloalkanones (77–97%), and lower yields from seven- and eight-membered cycloalkanones (50 and 85%, respectively).

**Table 1.** Synthesis of cycloalkanespirohydantoin **3** from cycloalkanones **9**



Entry	<b>3</b>	n	R <sup>1</sup>	R <sup>2</sup>	Yield [%] <sup>a</sup>	MW temperature [°C] <sup>b</sup>	MW yield [%] <sup>c</sup>
1	<b>a</b>	0	H	H	20	140	80
2	<b>b</b>	1	H	H	59	120	94
3	<b>c</b>	1	CH <sub>3</sub>	H	16	120	77
4	<b>d</b>	1	H	CH <sub>3</sub>	25	140	97
5	<b>e</b>	2	H	H	87	140	50
6	<b>f</b>	3	H	H	100	140	85

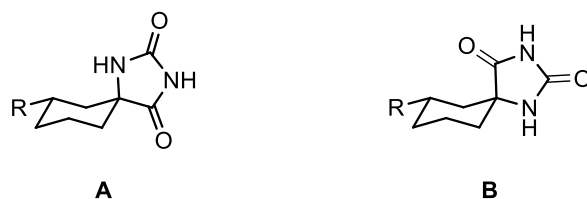
<sup>a</sup>Obtained at classic Bucherer-Berg condition.<sup>20</sup>

<sup>b</sup>Optimum temperature for microwave assisted synthesis.

<sup>c</sup>Conditions of synthesis by microwave: 8 min, 100 Watts.

Moreover, a methyl group at C2 of the cyclohexanone in **9c** lowers the electrophilicity of the carbonyl group more than a methyl group in position C3 as in **9d**. Also, steric hindrance by the methyl group at C2 in **9c** may explain the low yield of **3c** as compared to that of **3d**.

Compounds **3c** and **3d** are expected to form a mixture of diastereomers ( $\alpha$ -form **A** and  $\beta$ -form **B**, Figure 3), but only one stereoisomer was apparent by NMR.



**Figure 3.** Diastereomers expected for compounds **3c** and **3d**.

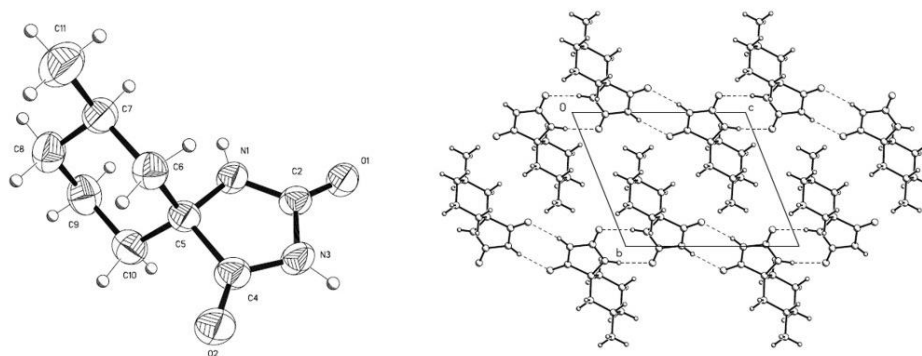
It is well documented that the  $\alpha$ -form **A** of hydantoin predominates when prepared from substituted cycloalkanones by the Bucherer synthesis, whereas the  $\beta$ -isomer **B** predominates when the Strecker synthesis is used.<sup>21</sup> It is generally assumed that alkyl-substituted cycloalkanones form exclusively the  $\alpha$ -form of cycloalkanespirohydantoin.<sup>22,23</sup>

This is confirmed by the ORTEP structure of spirohydantoin **3d** obtained by X-ray analysis (Table 2). Figure 4 shows the X-ray diffraction structures; Table 3 gives the geometry of the intermolecular hydrogen bonds.

**Table 2.** Crystal data for 7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione **3d**<sup>a</sup>

Crystal system	Triclinic
Space group	<i>P</i> -1
Unit cell dimensions	
a, [Å]	6.025(1)
b, [Å]	8.775(2)
c, [Å]	10.432(2)
Z	2
Density <sub>calcd.</sub> , mg·m <sup>-3</sup>	1.271
Reflections collected	5203
Independent reflections	1742 [R(int) = 0.0673]
Data/restraints/parameters	1742/1/125
Residual factors [I>2 $\sigma$ (I)]	R1 = 0.0371, wR2 = 0.0997

<sup>a</sup>Single crystals of **3d** grown by slow diffusion of methanol in a water solution.



**Figure 4.** X-ray diffraction structure of spirohydantoin **3d**.

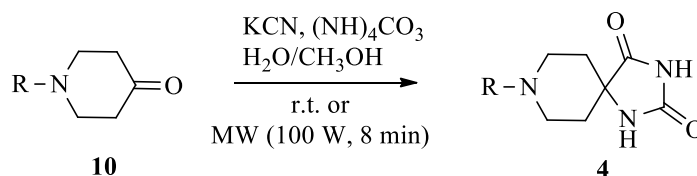
**Table 3.** Dimensions of the hydrogen bonds in compound **3d**

D–H···A	d(D–H) [Å]	d(H···A) [Å]	d(D···A) [Å]	∠(DHA) [°]
N(1)–H(1)···O(1)#1	0.846(14)	2.015(14)	2.8567(15)	172.6(14)
N(1)–H(1)···O(1)#2	0.824(14)	2.066(14)	2.8763(15)	167.5(14)

Symmetry transformations used to generate equivalent atoms: #1 -x,-y+2,-z #2 -x,-y+2,-z+1.

Under thermal conditions, piperidones **10a–c** were treated with KCN and  $(\text{NH}_4)_2\text{CO}_3$  to give moderate yields of piperidinespirohydantoin **4a–c** (Table 4).

**Table 4.** Synthesis of piperidinespirohydantoin **4** from piperidones **10**



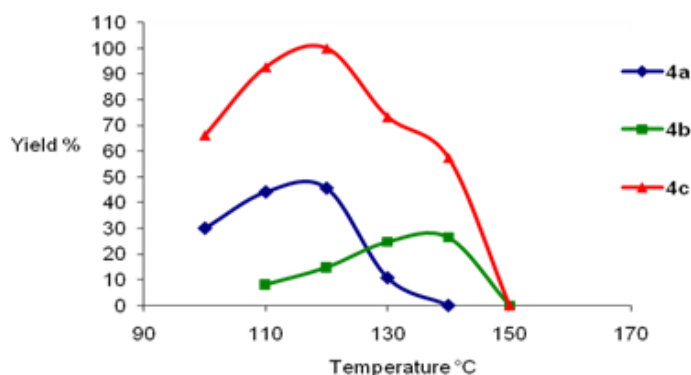
Entry	<b>4</b>	R	Yield [%] <sup>a</sup>	MW temperature [°C] <sup>b</sup>	MW yield [%] <sup>c</sup>
1	<b>a</b>	H	57	120	46
2	<b>b</b>	CH <sub>3</sub>	26	140	35
3	<b>c</b>	PhCH <sub>2</sub>	61	130	~99

<sup>a</sup>Obtained by classic Bucherer-Berg condition.<sup>20</sup>

<sup>b</sup>Optimum temperature for microwave assisted synthesis.

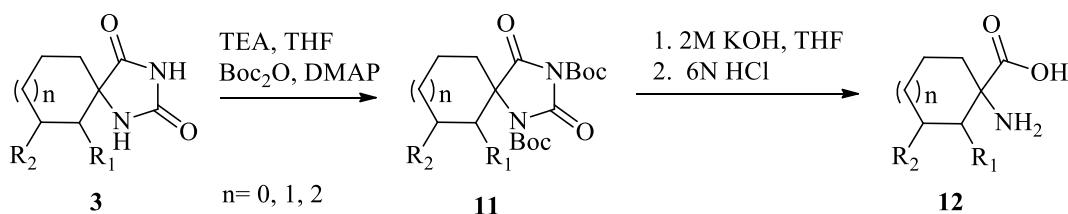
<sup>c</sup>Microwave assisted conditions: 8 min, 100 Watts.

Piperidinespirohydantoin **4a–c** were obtained by maintaining the time at 8 min at different temperatures (Figure 5); maximum yields were obtained at 120, 140, and 130 °C, respectively (Table 4). Under microwave irradiation conditions spirohydantoin **4c** was obtained quantitatively under same conditions.



**Figure 5.** Study of temperature and yields for spirohydantoin **4**.

Finally, cycloalkanespirohydantoin **3a–e** were converted into restricted amino acids **12** by protecting with di-*tert*-butyl dicarbonate to obtain *N,N'*-diprotected spirohydantoin **11a–e**, which were hydrolyzed under basic conditions followed by strong acidification (Scheme 3).



**Scheme 3.** Synthesis of restricted amino acids **12** from cycloalkanespirohydantoin **3**.

Hydantoin requires harsh conditions for hydrolysis, thus compromising the ability to generate side-chain protected polyfunctional amino acids. This problem was partially overcome by Rebek and coworkers,<sup>24</sup> who discovered that *N,N'*-bis(*tert*-butyloxycarbonyl)hydantoin can be hydrolyzed under milder conditions.

Without prior isolation, compounds **11** were hydrolyzed in a biphasic mixture of THF and aqueous 2.0 M KOH solution at room temperature to promote the clean separation of the restricted amino carboxylate **12** (in the aqueous phase) from the hydrolysis byproduct di-*tert*-butyliminodicarboxylate (in the THF layer).

Amino acids **12a–c** were obtained in quantitative yields, while the  $\alpha$ -amino acids **12d** and **12e** gave 80% and 89% yields, respectively (Table 5). The identity of the restricted  $\alpha$ -amino acids **12** was confirmed by NMR and by electrospray ionization mass spectrometry (ESIMS).

**Table 5.** Yields of restricted amino acids **12**

Entry	<b>12</b>	n	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>a</sup>
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					[%]
1	<b>a</b>	0	H	H	~99
2	<b>b</b>	1	H	H	~99
3	<b>c</b>	1	CH <sub>3</sub>	H	~99
4	<b>d</b>	1	H	CH <sub>3</sub>	80
5	<b>e</b>	2	H	H	89

## Experimental Section

**General.** All reagents were used in the highest quality available without further purification. The solvents for column chromatography were used as obtained from commercial suppliers. Infrared spectra (FTIR) were recorded on a Perkin Elmer FT-IR 1600 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra (at 200 and 50 MHz, respectively) of CDCl<sub>3</sub> solutions with TMS as internal standard were recorded on a Varian Mercury 200 MHz Spectrometer. Liquid chromatograms were obtained on an Agilent 1100 Series LC with a reverse phase ZORBAX sβ-C18 column (5 mm, 3 x 150 mm) and MSD Trap. Electrospray ionization mass spectra (ESIMS) were obtained with an ion trap. HRMS were obtained in an Agilent LCTOF (2006), a high resolution TOF analyzer with Windows XP based OS and APCI/ESI ionization. Melting points were obtained with an Electrothermal 88629 apparatus. Microwave assisted synthesis was carried out in a CEM Discover™ Focused Synthesizer.

### Synthesis of hydantoin (3) and (4) under microwave conditions. General method A

10 mL pressure-rated vial was charged with the ketone (1.0 equiv), ammonium carbonate (2.15 equiv), methanol (2 mL), and deionised water (1 mL). The mixture was stirred at room temperature until the solid was dissolved. A solution of potassium cyanide was added (2.10 equiv) in water (1 mL). The vial was sealed and irradiated at 100 watts for 8 min to rise to the desired temperature. The conversion of cycloalkanone into spirohydantoin was monitored by IR. Excess of solvent was eliminated under reduced pressure and the yellow solid was washed with deionised water (4 x 25 mL). The product was dried at reduced pressure to obtain the pure spirohydantoin.

**1,3-Diazaspiro[4.4]nonane-2,4-dione (3a).** Cyclopentanone (0.20 g, 2.37 mmol), ammonium carbonate (0.49 g, 5.11 mmol) and potassium cyanide (0.32 g, 4.98 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.29 g, 1.90 mmol, 80%); mp 195–197 °C, lit.<sup>8</sup> mp 196–197 °C. IR (KBr): 3211, 1778, 1735 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.14 (s, 1H), 1.71 (m, 8H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 179.0 (s), 156.0 (s), 68.2 (s), 37.2 (2 x t), 24.7 (2 x t). ESIMS: *m/z* 152.8 [M-H]<sup>+</sup>.

**1,3-Diazaspiro[4.5]decane-2,4-dione (3b).** Cyclohexanone (0.20 g, 2.03 mmol), ammonium carbonate (0.42 g, 4.38 mmol) and potassium cyanide (0.28 g, 4.27 mmol) were dissolved in a methanol/water solution (50:50). Yellow solid (0.32 g, 1.91 mmol, 94%); mp 206–208 °C, lit.<sup>8</sup> mp 207–209 °C. IR (KBr): 3200, 1773, 1734, 1410 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.5 (s, 1H), 8.37 (s, 1H), 1.50 (m, 10H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 178.3 (s), 156.1 (s), 62.1 (s), 33.3 (2 x t), 24.6 (2 x t), 21.0 (t). ESIMS: *m/z* 190.8 [M+Na]<sup>+</sup>. ESIMS: *m/z* 168.9 [M+H]<sup>+</sup>.



**6-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (3c).** 2-Methylcyclohexanone (0.20 g, 1.63 mmol), ammonium carbonate (0.34 g, 3.51 mmol) and potassium cyanide (0.22g, 3.44 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.23 g, 1.26 mmol, 77%); mp 202–204 °C, lit.<sup>17a</sup> mp 200–202 °C. IR (KBr): 3506, 1773, 1727, 1426 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.21 (s, 1H), 1.55 (m, 7H), 1.25 (q, *J* = 9.0 Hz, 1H), 0.66 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 178.2 (s), 156.9 (s), 66.1 (s), 35.9 (t), 34.4 (d), 29.3 (t), 25.2 (t), 20.8 (t), 15.6 (q). ESIMS: *m/z* 180.7 [M–H]<sup>+</sup>. HRMS: calcd. for [C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>+H]<sup>+</sup> 183.1134; found 183.1136.

**7-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (3d).** 3-Methylcyclohexanone (0.20 g, 1.63 mmol), ammonium carbonate (0.34 g, 3.51 mmol) and potassium cyanide (0.22 g, 3.44 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.29 g, 1.58 mmol, 97%); mp 252–254 °C. IR (KBr): 3196, 1766, 1723, 1404 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.5 (s, 1H), 8.41 (s, 1H), 1.55 (m, 8H), 1.25 (q, *J* = 12.6 Hz, 1H), 0.85 (d, *J* = 6.2 Hz, 3H). <sup>13</sup>C NMR (50 Hz, DMSO-*d*<sub>6</sub>): δ: 178.3 (s), 156.2 (s), 62.7 (s), 41.1 (t), 33.1 (t), 32.6 (t), 26.9 (d), 22.0 (t), 20.7 (q). ESIMS: *m/z* 181.6 [M–H]<sup>+</sup>.

**1,3-Diazaspiro[4.6]undecane-2,4-dione (3e).** Cycloheptanone (0.20 g, 1.78 mmol), ammonium carbonate (0.37 g, 3.83 mmol) and potassium cyanide (0.24 g, 3.75 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.16 g, 0.89 mmol, 50%); mp 191–193 °C, lit.<sup>8</sup> mp 189–191 °C. IR (KBr): 3281, 1769, 1710, 1399 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.20 (s, 1H), 1.77 (d, *J* = 12.4 Hz, 2H), 1.62 (m, 10H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 184.8 (s), 161.5 (s), 69.5 (s), 41.9 (2 t), 33.8 (2 t), 27.2 (2 t). ESIMS: *m/z* 180.8 [M–H]<sup>+</sup>.

**1,3-Diazaspiro[4.7]dodecane-2,4-dione (3f).** Cyclooctanone (0.20 g, 1.58 mmol), ammonium carbonate (0.33 g, 3.40 mmol) and potassium cyanide (0.22 g 3.32 mmol) were dissolved in a methanol/water solution (50:50). Yellow solid (0.26 g, 1.34 mmol, 85%); mp 224–226 °C, lit.<sup>8</sup> mp 221–223 °C. IR (KBr): 3197, 1776, 1730, 1410 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 9.16 (s, 1H), 2.82–2.48(m, 14 H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ: 184.2 (s), 161.3 (s), 69.0 (s), 37.0 (2 t), 32.6 (2 t), 28.9 (2 t), 26.3 (CH<sub>2</sub>). ESIMS: *m/z* 194.7 [M–H]<sup>+</sup>.

**1,3,8-Triazaspiro[4.5]decane-2,4-dione (4a).** Piperidone (0.20 g, 1.05 mmol), ammonium carbonate (0.22 g, 2.27 mmol) and potassium cyanide (0.14g, 2.22 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.07 g, 0.42 mmol, 46%); mp >260 °C. IR (KBr): 3193, 1776, 1735, 1412 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.6 (s, 1H), 8.38 (s, 1H), 3.09 (m, 4H), 2.14 (d, *J* = 14.4 Hz, 2H), 1.95 (d, *J* = 13.8 Hz, 2H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ: 180.2 (s), 160.0 (s), 61.1 (s), 42.2 (2 t), 31.5 (2 t). ESIMS: *m/z* 170 [M+H]<sup>+</sup>. HRMS: calcd. for [C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>+H]<sup>+</sup> 170.0930; found 170.0931.

**8-Methyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (4b).** *N*-methyl-4-piperidone (0.20 g, 1.76 mmol), ammonium carbonate (0.36 g, 3.79 mmol) and potassium cyanide (0.24 g, 3.71 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid (0.11 g, 0.62 mmol, 35%); mp >260 °C. IR (KBr): 3190, 1771, 1721, 1401 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 10.6 (s, 1H), 8.38 (s, 1H), 3.36 (m, 1H), 2.67 (d, *J* = 11.8 Hz, 2H), 2.20 (d, *J* = 2.6 Hz, 2H), 2.17 (m, 4H), 2.14 (d, *J* = 2.6 Hz, 2H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 178.2 (s), 156.3 (s), 59.7 (s), 50.1 (2 t), 45.8 (q), 33.1 (2 t). ESIMS: *m/z* 184.1 [M+H]<sup>+</sup>. HRMS: calcd. for [C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>+H]<sup>+</sup> 184.1086; found 184.1089.

**8-Benzyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (4c).** *N*-benzyl-4-piperidone (0.2 g, 1.05 mmol), ammonium carbonate (0.22 g, 2.27 mmol) and potassium cyanide (0.14 g, 2.22 mmol) were dissolved in a methanol/water solution (1:1). Yellow solid. (0.25 g, 0.94 mmol, ~99%); mp 259–261 °C. IR (KBr): 3193, 1776, 1735, 1412 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, DMSO-*d*<sub>6</sub>): δ 8.39 (s, 1H), 7.29 (m, 5H), 2.72 (m, 2H), 2.28 (t, *J* = 11.0 Hz, 2H), 2.00 (s, 2H), 1.80 (t, *J* = 12.4 Hz, 2H), 1.47 (d, *J* = 13.6 Hz, 2H). <sup>13</sup>C NMR (50 MHz, DMSO-*d*<sub>6</sub>): δ 178.2 (s), 156.4 (s), 138.5 (s), 128.5 (2 d), 128.1 (2 d), 126.8 (d), 61.9 (s), 60.1 (t), 48.1 (2 t), 33.1 (2 t). ESIMS: *m/z* 258 [M–H]<sup>+</sup>. HRMS: calcd. for [C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>+H]<sup>+</sup> 260.1399; found 260.1403.

### 1-Aminocyclopentanecarboxylic acid (12a). Typical procedure

A round bottom flask equipped with an argon inlet adapter, glass stopper and an overhead mechanical stirrer was charged with a suspension of the 1,3-diazaspiro[4.5]decane-2,4-dione **3a** (1.0 g, 6 mmol) in 30 mL of dry THF.<sup>24,25</sup> Triethylamine (0.60 g, 6 mmol) was added in one portion and the resulting white suspension was stirred for 30 min. di-*tert*-butyl dicarbonate (6.5 g, 29 mmol) was added dropwise, followed by 4-dimethylaminopyridine (DMAP) (7.08 mg, 0.06 mmol). Six additional portions of DMAP were added at 12 h intervals during the course of the reaction. The reaction mixture was stirred vigorously for 72 h. Then, potassium hydroxide solution (2.0 M, 30 mL) was added in one portion. The reaction mixture was stirred for 6 h and then poured into a 125 mL separatory funnel. The layers were allowed to separate over 45 min, and the aqueous layer was then drained into a 250-mL round-bottomed flask. This solution was cooled to 0 °C, the pH was adjusted to 8.0 by the slow addition of 6.0 N HCl solution. The resulting mixture was further acidified to pH 6.5 by slow addition of 2.0 N HCl solution. The white precipitate, which appeared was collected by filtration on a Buchner funnel, and the filtrate was concentrated to a volume of 60 mL to furnish additional precipitate, which was collected by filtration. The portions of white solid were combined, dried at room temperature under reduced pressure to obtain the α-amino acid **12a** as a pure white solid (0.77 g, 6.0 mmol, ~99%); mp 300 °C, lit.<sup>19</sup> mp 301–302 °C. IR (KBr): 3471, 1623, 1577, 1399 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, D<sub>2</sub>O): δ 2.41 (m, 2H), 1.94 (m, 6H). <sup>13</sup>C NMR (50 MHz, D<sub>2</sub>O): δ 177.6 (s), 67.3 (s), 38.9 (2 t), 27.6 (2 t). ESIMS: *m/z* 130 [M+H]<sup>+</sup>.

**1-Aminocyclohexanecarboxylic acid (12b).** White solid (0.86 g, 6.0 mmol, ~99%); mp >300 °C, lit.<sup>19</sup> mp 308–309 °C. IR (KBr): 3384, 1616, 1528, 1410 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 Hz, D<sub>2</sub>O): δ 2.00 (m, 2H), 1.75 (m, 5H), 1.45 (m, 3H). <sup>13</sup>C NMR (50 Hz, D<sub>2</sub>O): δ 163.2 (s), 63.6 (s), 34.1 (2 t), 26.4 (t), 22.9 (t). ESIMS: *m/z* 143.9 [M+H]<sup>+</sup>.

**1-Amino-2-methylcyclohexanecarboxylic acid (12c).** White solid (0.94 g, 6.0 mmol, ~99%); mp >300 °C, lit.<sup>18</sup> mp 304–305 °C. IR (KBr): 3446, 1715, 1576, 1381 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, D<sub>2</sub>O): δ 2.16 (m, H), 1.90 (m, H), 1.51 (m, H), 1.07 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (50 MHz, D<sub>2</sub>O): δ 176.8 (s), 67.1 (s), 37.7 (t), 35.1 (d), 30.7 (t), 26.9 (t), 22.1 (t), 18.5 (q). ESIMS: *m/z* 339 [2M+Na+H]<sup>+</sup>.

**1-Amino-3-methylcyclohexanecarboxylic acid (12d).** White solid (0.75 g, 4.8 mmol, 80%); mp >300 °C. IR (KBr): 3442, 1657, 1579, 1442 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 MHz, D<sub>2</sub>O): δ 1.56 (m, 5H), 1.31 (s, 3H), 1.19 (m, 2H), 0.73 (d, *J* = 6.6 Hz, 1H), 0.53 (d, *J* = 6.6 Hz, 3H). <sup>13</sup>C NMR (50 MHz, D<sub>2</sub>O): δ 178.6 (s), 58.7 (s), 44.4 (t), 35.1 (t), 34.7 (t), 26.9 (d), 20.5 (q), 19.6 (t). ESIMS: *m/z* 339 [2M+Na+H]<sup>+</sup>.

**1-Aminocycloheptanecarboxylic acid (12e).** White solid (0.84 g, 5.34 mmol, 89%); mp >300 °C, lit.<sup>19</sup> mp >300 °C. IR (KBr): 3481, 1652, 1590, 1458 cm<sup>-1</sup>. <sup>1</sup>H NMR (200 Hz, D<sub>2</sub>O): δ 1.98 (m, 2H), 1.61 (d, *J* = 12.6 Hz, 2H), 1.42 (br s, 8H). <sup>13</sup>C NMR (50 MHz, D<sub>2</sub>O): δ 177.3 (s), 64.9 (s), 36.7 (2 t), 30.9 (2 t), 23.7 (2 t). ESIMS: *m/z* 387 [2M+Na]<sup>+</sup>.

## Conclusions

An optimized microwave-assisted methodology was developed for the synthesis of spirohydantoins **3** and **4**. The cycloalkanespirohydantoins **3** were used for the synthesis of restricted α-amino acids **12** with very good overall yields starting from the cycloalkanones **9**. By this method restricted α-amino acids were obtained in a fast and effective manner.

## Acknowledgements

We are grateful to Consejo Nacional de Ciencia y Tecnología, México (CONACyT, GRANT No. SEP-2004-CO1-47895) and Dirección General de Educación Superior Tecnológica (DGEST) for support of this project. Edgar A. Reynoso thanks CONACYT for a graduate scholarship.

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